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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,927	05/30/2001	Robert H. Getzenberg	076333-0240	6351

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 11/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,927	GETZENBERG, ROBERT H.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *2-6,8,9 and 13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of group VI, claims 1, 11, 12 in part and claims 7 and 10 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 2-6, 8-9, 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made in Paper No. 8.

3. Claims 1, 11, 12 in part and claims 7 and 10 are under examination. Claims 1, 11, and 12 will be examined to the extent the antibody binds BLCA-6. Claim 10 is being examined as dependent from claim 7 not claim 4 as SEQ ID NO:4 is part of BLCA-6 (see page 33, lines 28-29).

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate application 09/143,369 and 08/742, 850 are now U.S. Patents.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Claim Objections

5. Claims 1, 11, 12, and 10 are objected to because of the following informalities:

a. Claims 1, 11, and 12 contain non-elected subject matter.

b. Claim 10 depends from non-elected claim 4. For examination claim 10 is being interpreted as depending from claim 7.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 7, 11, 10, 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 12 are indefinite for reciting in claims 1 and 12 the phrase "antigen thereof" for the exact meaning of the phrase is not known. An antigen is a molecule to which an antibody binds. How does the antigen differ from the nuclear matrix protein? Does the phrase "antigen thereof" encompass chemically modified proteins, proteins with labels, fusion proteins, etc.. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

b. Claim 12 is indefinite for reciting "is not elevated in subjects" for the exact meaning of the phrase is not known. It is not clear as to what extent the term "elevated"

is meant and it is not clear by whom or what criteria decides "not elevated". Is the protein level, activity, antigenicity, turnover, half-life, etc which is elevated? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

c. Claims 1, 7, 10, 11 are indefinite because it is not clear what molecular weight the BLCA-6 protein has. As evidenced from Getzenberg et al (Cancer Research 56:1690-94, 1996), which appears to be the same BLCA-6 named nuclear matrix protein as that in the specification, however, Getzenberg et al protein has a molecular weight of 31 kD as opposed to the instant claimed protein which has 22 kD. Thus, it appears that there is a discrepancy in the molecular weight of the BLCA-6 protein. It is unclear what molecular weight the BLCA-6 has.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 7, 10, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibody which specifically binds to a nuclear matrix protein, wherein said nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells, and the nuclear matrix protein is BLCA-6, does not reasonably provide enablement for any antibody that specifically binds to any nuclear matrix protein or antigen thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims broadly encompass an antibody that specifically binds to a nuclear matrix protein or an antigen thereof. The claims encompass a myriad of antibodies which bind an infinite number of antigens as defined by "an antigen thereof". The claims encompass antibodies which bind to fusion proteins containing nuclear matrix proteins, nuclear matrix proteins with labels, nuclear matrix proteins that are chemically modified, etc..

The specification teaches production of an antibody which binds to the BLCA-6 protein, specifically the antibody binds to BCLA-6 which comprises SEQ ID NO:4 (page 33). The specification teaches the detection of BLCA-4 in bladder tissue samples but was absence in normal tissue (page 35, lines 4-28).

The specification does not enable all of the myriad of variants and conjugates of the BLCA-6 protein that are encompassed by the claims as well as all of the antibodies that would be specific for the variants.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins as well as antibodies broadly encompassed by the claims and the claims broadly encompass a significant number of species.

It is well known in the art that amino acid changes alter the function as well as the ability of an antibody to bind to a protein this is demonstrated by Colman (Research in Immunology 145:33-36, 1994) which states that even conservative changes in the amino acid sequence may abolish binding of the antibody (see page 35). In addition , Lederman et al (Molecular Immunology 28:1171-81, 1991) teach that substitution of one amino acid in a protein ablates binding of the antibody to the antigen.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability as evidenced by Colman and Lederman et al associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Amending the claims to recite wherein the antibody specifically binds to a nuclear matrix protein, wherein said nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells, wherein the nuclear matrix protein is BLCA-6 or

similar language fully supported by the specification as originally filed would be sufficient to obviate this rejection.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1, 7, 10, 12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 7, 10, 12, as written, do not sufficiently distinguish over antibodies as they exists naturally because claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and binding compositions and the structure of naturally occurring antibodies

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated or purified" antibody or similar language would obviate this rejection.

Priority

12. Claim 12 recites an antibody that specifically binds to a nuclear matrix protein or an antigen thereof, wherein said nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells and is not elevated in subjects afflicted with cystitis.

No evidence for support or written description of the claimed limitations of the "elevated in subjects afflicted with cystitis" is seen in applications 60/006,226 or 80/742,850 for which the instant application claims priority under 35 U.S.C. 120. Therefore, claim 12 is granted the priority date of the filing date of 09/143,369 application, which is 08/28/98.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 12 is rejected under 35 U.S.C. 102(b) as anticipated by Getzenberg et al (Cancer Research 56:1690-4, 1996).

The claim recites an antibody that specifically binds to a nuclear matrix protein wherein the nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells and is not elevated in subjects afflicted with cystitis.

Getzenberg et al teach nuclear matrix proteins which are present in bladder cancer cells and not in normal bladder cells (see Table 2 for BLCA-6) and the proteins have been isolated and are being used to raise antibodies to the proteins (see pages 1693-4). It would be inherent that the protein of Getzenberg et al is also not elevated in patients with cystitis. This reference is being applied because of the priority date of claim 12.

15. Claims 1, 7, 10, 11, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Briggman et al (Proceedings of the American Association for Cancer Research, Vol. 35 p15, #89, March 1994) as evidenced by Stedman's Medical Dictionary 1995, Williams and Wilkins.

The claims recite an antibody that specifically binds to a nuclear matrix protein or antigen thereof, wherein said nuclear matrix protein is present in cancerous bladder cells but absent in normal bladder cells, wherein the nuclear matrix protein is BLCA-6 having a molecular weight of about 22 kD and a pI of about 8.00 and wherein the protein comprises the amino acid sequence of SEQ ID NO:4 (which is a 12 residue amino acid sequence) an and wherein the antibody is a monoclonal antibody. Further, the claims recite an antibody to a nuclear matrix protein which is not elevated in subjects afflicted with cystitis.

Briggman et al teach an immunoassay with monoclonal antibodies directed to a nuclear matrix protein (NMP) in the urine of patients with bladder cancer but absent in normal patients and in patients with benign diseases of the urinary tract. Stedmans's

Medical Dictionary teaches cystitis as "inflammation of the urinary bladder" and one of skill in the art would reasonably conclude that cystitis i.e. "inflammation of the urinary bladder" would include benign diseases of the urinary tract.

Therefore, it is the Examiner's position that Briggman et al have produced antibodies which bind to a nuclear matrix protein , NMP, present in cancerous bladder cells but absent in normal bladder cells and in patients with benign diseases of the bladder that are directed to the same antigen that the claimed antibodies bind. One of ordinary skill in the art would reasonably conclude that Briggman et al's antibodies also bind to the same nuclear matrix protein BLCA-6 which is in cancerous bladder cells as the protein bound by the antibodies claimed and, therefore, it appears that Briggman et al have produced antibodies that are identical to the claimed antibody and which binds the BLCA-6 protein. Briggman et al is silent as to what nuclear matrix protein(s) the antibodies bind to and what structural features the nuclear matrix proteins (NMP) possess. Consequently, comparison of the claimed antibodies with the prior art antibodies is difficult since the Office is not equipped to manufacture the claimed antibodies and/or prior art antibodies that appear to be related and conduct comparisons. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Briggman et al, the burden of proof is upon the Applicants to show an unobvious distinction between the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Getzenberg et al (Cancer Research 56:1690, 1994) and further in view of Campbell (Monoclonal antibody technology Elsevier Science publishers, chapter 1, pages 1-32, 1986).

Claim 12 has been described supra.

Getzenberg et al has been described supra. Getzenberg et al does not exemplify the production of the antibody. This deficiency is made up for in the teachings of Campbell.

Campbell et al teach methods of making monoclonal antibodies to proteins.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody to the protein of BLCA-6 of Getzenberg et al with the method of Campbell.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an antibody to the protein of BLCA-6 of Getzenberg et al with the method of Campbell because Getzenberg et al teach that the protein was isolated and antibodies were made to the protein and Campbell teach that it is customary now for any group working on a macromolecule to both clone the gene coding for it and make antibodies to it (see page 29).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879